Case report

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REFRACTORY SEIZURES AFTER ENDOSULFAN INGESTION IN A 12-YEAR-OLD BOY

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We describe the case of a 12 year old boy who presented with acute endosulfan poisoning. On enquiry, the parents gave a history of suicidal consumption of endosulfan. On examination the patient was in status epilepticus, and his general condition was poor. After initial clinical and laboratory assessment the patient was treated with routine management of acute poisoning in the form of gastric lavage where the gastric contents were aspirated initially and the contents were collected for chemical analysis. The lavage was performed with activated charcoal. Since the seizures were non responsive to conventional first line anticonvulsant drugs for 30 minutes, we characterized the case as refractory status epilepticus. In view of the failure of above medication to control the seizures, further management for refractory seizures was initiated, the patient was intubated and put on mechanical ventilation with a loading dose of thiopentone sodium (5 mg/kg). The seizures ceased in 30 minutes. The rate of the infusion was gradually reduced and stopped as flickering movements subsided. After the 5th day the condition of the patient improved and he regained consciousness and was slowly weaned off the ventilator. The patient was discharged on the 10th day from admission in an ambulatory state with no seizures and no neurological deficits. **Conclusion -** We suggest the use of other antiepileptic drugs, such as thiopentone sodium, to treat refractory status epilepticus.

Key words: Endosulfan poisoning ▪ Refractory seizures ▪ Thiopentone sodium

Introduction

Endosulfan is a highly toxic organochlorine pesticide used in agriculture that produces well known life threatening ne-

urological symptoms. Acute toxicity may result in permanent neurological impairment (1). Organochlorine pesticides antagonize the major inhibitory neurotransmitter, gamma amino butyric acid (GABA). Binding these pesticides to glycine and GABA -A gated chloride channels reduces influx of chloride ions, leading to neuronal hyper excitability and toxicity (2). Endosulfan also inhibits calmodulin- dependent Ca++ ATPase activity in the brain and cause fluctuations in the serotoninergic system and decreases activity of GABA on the neuronal membrane. The decrease in the activity of GABA releases the synaptic inhibition of the neurons and facilitates the excitation of neurons (3, 4). Endosulfan is both a substrate and inhibitor of the cellular efflux transporter P-glycoprotein (P-gp), which plays an important role in regulating xenobiotics crossing the blood brain barrier (5), thus endosulfan enters and persists in the extravascular compartment of the central nervous system with ongoing toxicity, despite low plasma levels. Characteristic clinical signs after acute exposure are indicative of central nervous system (CNS) disturbances or overstimulation. These signs include convulsion, which is a common, and the most severe manifestation along with nausea, vomiting, abdominal discomfort, hyperaesthesia of the mouth and face, tongue and extremities, headaches, agitation, hyperactivity, incoordination, confusion, dizziness and myoclonus. Endosulfan is toxic to the liver, kidneys and lungs, and can cause rhabdomyolysis in higher doses (6). There is scanty literature about endosulfan poisoning in India and overseas. Here we report a case of endosulfan intoxication with refractory status epilepticus in a twelve year old male child.

Case report

A 12 year old male child with no personal and family history of epilepsy had three episodes of seizures at 15 minute intervals before coming to the hospital and presented with status epilepticus. He had three episodes of vomiting prior to the convulsions. On enquiry, parents gave a history of suicidal consumption of endosulfan. On examination, the patient was in status epilepticus, his general condition was poor and he had a heart rate of 100/min, SpO_2 of 90% and blood pressure of 100/60 mm Hg. His pupils were normal. Detailed systemic examination revealed sinus tachycardia with normal heart sounds, and the rest of the systemic examination was within normal limits. Tests showed: hemoglobin 10.4 gm%, total leucocyte count 9400/mm^3, platelet count 235x10^9/l, random blood sugar 78 mg%, serum creatinine 0.8 mg%, blood urea 29 mg/dl, sodium 132 meq/l, potassium 3.6 meq/l. Urine microscopy was normal. Cerebrospinal fluid examination, chest radiogram, and electrocardiogram were within normal limits. The computed tomography scan was normal, while the electroencephalogram showed discharges in the bilateral frontal region.

After initial clinical and laboratory assessment, the patient was treated with routine management of acute poisoning in the form of gastric lavage, where the gastric contents were aspirated initially with the help of Ryle`s tube insertion, the contents were collected for chemical analysis and lavage was performed using activated charcoal. Management of status epilepticus was instituted with a loading dose of intravenous phenobarbitone (20 mg/kg), but the patient's seizures did not subside. Thereafter, a loading dose of injection phenytoin (20 mg/kg) was given, but the seizures were not controlled. Since the seizures were non responsive to conventional first line anticonvulsant drugs for 30 minutes, we characterized the case as refractory status epilepticus. In view of the failure of the above medications to control seizures, further management for refractory seizures was initiated,

the patient was intubated and put on mechanical ventilation, with a loading dose of thiopentone sodium (5 mg/kg) at a total dose of 150 mg diluted in 10 ml of water for injection given over 10 minutes, and the seizures stopped in 30 minutes. The patient continued to have flickering movements, for which a continuous infusion of thiopentone sodium (1mg/kg/hour) was started. The rate of the infusion was gradually reduced and stopped as the flickering movements subsided. After the 5th day the condition of the patient improved and he regained consciousness and was slowly weaned off the ventilator over the following 24 hours. The patient was discharged on the 10th day from admission in an ambulatory state with no seizures or any neurological deficits. Before discharge, an opinion was given on the patient by a psychiatrist since the patient had consumed endosulfan probably due to severe depression. The patient was put on anti-epileptics which were gradually tapered and stopped after 6 weeks, and now the patient is on regular follow-up with his previous state of health restored.

Discussion

Endosulfan is a chlorinated insecticide that causes central nervous system hyperstimulation. It is absorbed from the gastrointestinal tract, skin, and respiratory tract. The seizures caused by endosulfan poisoning have been classified as acute symptomatic or provoked seizures.

In our case the patient presented with severe vomiting followed by status epilepticus, agitation and hyperactivity due to CNS stimulation, with normal laboratory parameters. Status epilepticus refers to a condition in which there is a failure of the "normal" factors that serve to terminate a typical seizure. Status epilepticus that is refractory to treatment may be the result of several processes and has been attributed to a mechanistic shift from inadequate GABAergic inhibitory receptor-mediated transmission to excessive NMDA excitatory receptor mediated transmission (7). Refractory status epilepticus was the most common cause of death (75%) in studies by Kutluthan et al. and Patel et al. (4, 8). Refractory status epilepticus is defined as seizures, which last longer than 60 minutes, despite treatment with benzodiazepine and an adequate loading dose of an intravenous antiepileptic drug (9). Refractory status epilepticus that has not responded to hydantoins and/or phenobarbitone requires general anaesthesia, using either thiopentone or propofol (10). In our case, the patient did not respond to phenobarbitone and phenytoin and was thus put on thiopentone sodium, which was probably due to phenytoin being less effective in such cases given the effect of endosulfan on GABA receptors. Thiopentone is a short acting barbiturate and rapidly and easily crosses the blood brain barrier, as it is a lipophilic molecule. Thiopentone acts on the barbiturate binding site of the GABAA receptor directly, gates the chloride ion channel of the GABAA receptor and increases the opening frequency of the chloride ion channel. Sodium thiopentone is redistributed away from the central circulation towards muscle and fat tissue, due to its very high fat:water partition coefficient, leading to its metabolism to pentobarbital, 5-ethyl-5-(1'-methyl-3'-hydroxybutyl)-2-thiobarbituric acid, and 5-ethyl-5-(1'-methyl-3'-carboxypropyl)-2-thiobarbituric acid. The post-synaptic inhibitory effect of thiopentone and phenobarbitone causes an anaesthetic state, thereby controlling seizures, so our patient responded to thiopentone infusion and the seizures did not recur. Pulmonary toxicity associated with endosulfan poisoning has been reported as an important manifestation (6) but was not seen in our case. Hypoxia may also be secondary to aspiration of vomitus or respiratory failure (11). Our

patient was given ventilator care to prevent aspiration and due to the anaesthetic state caused by thiopentone. Since our patient`s electroencephalogram showed sharp wave discharges in the bilateral frontal, anticonvulsant therapy was started. As long term anti-epileptic treatment is not required with endosulfan poisoning, in our patient's case anti-epileptics were gradually tapered and stopped after 6 weeks.

To date there are insufficient data on the use of thiopentone sodium in endosulfan poisoning with refractory status epilepticus. More clinical studies should be conducted to establish the use of thiopentone sodium in endosulfan poisoning.

Conclusion

To prevent deaths from endosulfan poisoning, its usage must be restricted and even prohibited. Also health personnel should be aware of the potential risk of intoxicating themselves when treating such patients. Atropine and catecholamines should be avoided Hence we would suggest the use of other antiepileptic drugs, such as thiopentone sodium, to treat refractory status epilepticus to reduce morbidity and mortality, as there is no specific antidote.

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